

**The Key to the Closet is the Key to the Kingdom:  
A Common Lesson of Rare Diseases**

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Nearly twenty centuries ago, the Roman poet Juvenal wrote in *The Satires* about “a rare bird comparable to a black swan.” The notion of rarity enticed the mind in antiquity, and continues to do so in modernity - in medicine and in our daily lives. What are the lessons of rarity and specifically of rare diseases? Let us look closer and observe.

The place was London. The date - April 24, 1657. A letter arrived at the home of Dr. William Harvey, a man whose life was distinguished by one of the greatest discoveries in the history of medicine, the discovery of the circulatory system. But, the letter to Dr. Harvey from a Dutch physician, John Vlackveld of Harlem, had nothing to do with common problems of the heart or blood or circulation. The letter invited Dr. Harvey’s attention to the case of a gentleman with an extremely rare affliction of the urinary bladder. Dr. Harvey was old and in failing health, and could not assume the challenge, but he clearly recognized the value of such a noble pursuit. He reached for a piece of parchment, dipped his pen in the inkwell, and wrote these words: “Learned Sir, your much esteemed letter reached me safely in which you not only exhibit your kind consideration of me, but display a singular zeal in the cultivation of our art. The case of the plasterer to which you refer is indeed a curious one, and might supply a text for a lengthened commentary. But, it is in vain that you apply the spur to urge me at my present age to gird myself for any new investigation.”

While unavailable, Dr. Harvey, however, was not disinterested. He continued the letter in what might arguably be one of the most prophetic passages ever written in the history of medicine:

“It is even so,” he wrote, “Nature is nowhere accustomed more openly to display her secret mysteries than in cases where she shows traces of her workings apart from the beaten path; nor is there any better way to advance the proper practice of medicine than to give our minds to the discovery of the usual law of nature by the careful investigation of cases of rarer forms of disease. For it has been found in almost all things, that what they contain of useful or of applicable nature, is hardly perceived unless we are deprived of them, or they become deranged in some way.”

Centuries later, in an address delivered to The Medical Society of London on May 21, 1928, Sir Archibald Garrod, the father of metabolic disease, cited that monumental letter from William Harvey. In an engaging essay entitled, “The Lessons of Rare Maladies,” published in **The Lancet** the following week, Dr. Garrod paraphrased, “The study of nature’s experiments is of special value; and many lessons which rare maladies can teach could hardly be learned in other ways.”

Francis S. Collins, M.D., Ph.D., Director of The National Human Genome Research Institute said more recently, “While many of the genes we will initially be pursuing are responsible for rare disorders, what we learn from rare disorders often has profound consequences for our understanding of more common conditions.” But, why is that so? Why are rare conditions so instructive of more common ones?

To begin, rare diseases provide robust insight into complexity in biological systems. The specificity of the rare disease often permits a causative genetic factor to be isolated in a

complex regulatory network, thus identifying and defining the network itself. Such insight is often the catalyst for dissecting the structural organization and/or inter-dependent signaling networks that are influenced by common genetic variations and that lead to some of the most common diseases of mankind. Nature does not use different genes, molecules, and pathways for common conditions than it does for rare ones. Rather, it is often the rare disease that actually reveals which gene, molecule or pathways nature hijacks in its common infirmities. The key to the rare disease is often the key to the common one. The key to the closet is often the key to the kingdom.

As examples, studies of familial hypercholesterolemia, Lesch-Nyhan disease, fibrodysplasia ossificans progressiva, congenital malignant osteopetrosis, and Hutchinson-Gilford progeria, all exceedingly rare conditions, have revealed the causative genes not only for each of these rare disorders, but have also illuminated the molecular pathways for common disorders of cholesterol metabolism, uric acid metabolism, heterotopic ossification, osteoporosis, and aging respectively – diseases that in some cases affect tens of thousands of people worldwide, and in other cases, millions.

The examples, iterations and lessons of rare maladies are profound and endless. In a dazzling article on “a new grammar for drug discovery,” (**Nature** 437: 491-493, 2005), Mark Fishman and Jeffrey Porter discuss the value of rare diseases not only for illuminating common conditions, but also for drug discovery. “Historically pharmaceutical companies have not focused on these diseases, in some cases because the affected protein is not tractable to pharmaceutical approaches, and in others, perhaps,

because the number of people affected is small. But, the powerful role of a single gene in Mendelian disease can provide insight into complex diseases where the same gene accounts for part of the phenotype. Statin therapy, for example, was initially directed to patients with a genetic predisposition to excessive levels of blood cholesterol. But after the drugs efficacy and safety had been tested, the treatment was extended to a wider population of patients who had the same condition but due to many causes.” Once again, the key to the closet is the key to the kingdom.

In the last paragraph of his essay (**The Lancet**; May 26, 1928), Sir Archibald Garrod states, “We may feel sure that, in the future as in the past, there will be many who will try to solve the problems of the commoner diseases, the control of which is of vital interest to the community at large. Let us hope there will always be some who will seek to guess the riddles and to learn the lessons of rare maladies.” The implication, of course, is that in doing so, one may provide the clues to solve the more common conditions as well. How ironic and fortuitous that nature would construct such a universal key and place it not in the hands of the king, but in the hands of the custodian. The key to the closet is the key to the kingdom.

And, so we will end where we began with the letter from Dr. Harvey to Dr. Vlackveld, long before the era of gene identification or molecular discovery or recombinant technology. It was almost 350 years ago in London, when Dr. Harvey wrote those words that have not been improved upon since. “It is even so. Nature is nowhere accustomed more openly to display her secret mysteries than in cases where she shows traces of her

workings apart from the beaten path; nor is there any better way to advance the proper practice of medicine than to give our minds to the discovery of the usual law of nature by the careful investigation of cases of rarer forms of disease.” The key to the closet is the key to the kingdom. It is even so.